IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Lorens et al.
Application No. 10/696,909
Filed: October 29, 2003
Confirmation No. 9257
For: MODULATORS OF ANGIOGENESIS AND TUMORIGENESIS

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Examiner: Peter J. Reddig
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APPLICANTS' APPEAL BRIEF

This is an appeal brief filed under 37 C.F.R. § 41.37. A Notice of Appeal was received by the U.S. Patent and Trademark Office on September 23, 2008, making the Appeal Brief due on or before November 23, 2008. As November 23, 2008, falls on a Sunday, the Appeal Brief is timely filed on or before **November 24, 2008**. In accordance with 37 C.F.R. § 41.20(b)(2), this Appeal Brief is being filed together with the required fee of $270. The Commissioner is hereby authorized to charge any deficiency in the required fee or to credit any overpayment to Deposit Account No. 02-4550.

I. REAL PARTY IN INTEREST

The real party in interest is Rigel Pharmaceuticals, Inc., the assignee of record of the present application (recorded at Reel 015425, Frames 0299-0303, December 3, 2004).

II. RELATED APPEALS AND INTERFERENCES

There are no related proceedings.

III. STATUS OF CLAIMS

Claims 1, 12, 14-18, 27, 41-44, and 54-61 are pending. Claims 2-11, 13, 19-26, 28-40, and 45-53 have been canceled. Claims 1, 12, 14-18, 27, 41-44, and 54-61 have been rejected, and are appealed. The pending claims are included in the attached Claims Appendix.

IV. STATUS OF AMENDMENTS

An amendment was filed with the Notice of Appeal on September 23, 2008 in response to the Non-final Office Action of June 23, 2008. Applicants understand that this amendment will be entered as a matter of right (as a response to a Non-final Office action). This was confirmed by Examiner Reddig in a voice mail to Applicants' representative Susan W. Graf on November 7, 2008.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The present invention stems from the discovery that Axl kinase (*e.g.*, SEQ ID NO: 4) is involved in angiogenesis. This discovery was made through Applicants' demonstration that treatment of human primary endothelial cells with Axl RNAi inhibited haptotaxis and tube formation of the endothelial cells, thus indicating Axl's role in angiogenesis. As embodied by claim 1, the invention at issue relates to a method for identifying a compound that inhibits angiogenesis by "assaying *in vitro* kinase activity of an Axl polypeptide comprising an amino acid sequence with greater than about 95% identity to full length SEQ ID NO: 4 in the presence of the compound" and "performing a cell-based assay in an endothelial cell comprising said Axl polypeptide in the presence of the compound, wherein inhibition of the *in vitro* kinase activity of the Axl polypeptide in the presence of the compound and inhibition of the angiogenesis phenotype in the cell-based assay in the presence of the compound identifies the compound as a

compound that inhibits angiogenesis." See, *e.g.,* specification, original claim 1; page 8, line15 to page 9, line 8; page 9, lines 32-34; page 30, lines 4-29.

As embodied by claim 27, the invention at issue also relates to a method for identifying a compound that inhibits angiogenesis by "contacting the compound with an endothelial cell that expresses a recombinant Axl polypeptide comprising an amino acid sequence with greater than about 95% identity to full length SEQ ID NO: 4" and "performing a cell-based assay, which assay produces an angiogenesis phenotype, wherein inhibition of the angiogenesis phenotype in the cell-based assay in the presence of the compound identifies the compound as a compound that inhibits angiogenesis." See, *e.g.,* specification at page 9, lines 32-34; page 31, line 22 to page 33, line 12.

As further embodied by claim 56, the invention at issue also relates to a method for identifying a compound that inhibits angiogenesis by "contacting the compound with an endothelial cell that expresses a recombinant Axl polypeptide comprising an amino acid sequence with greater than about 95% identity to full length SEQ ID NO: 4" and "assaying the kinase activity of the Axl polypeptide, wherein inhibition of the kinase activity of the Axl polypeptide in the presence of the compound identifies the compound as a compound that inhibits angiogenesis." See, *e.g.,* specification at page 9, lines 32-34; page 31, lines 22-32.

VI. GROUNDS OF REJECTION FOR REVIEW

Claims 1, 12, 14-18, 27, 41-44, and 55-61 are rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the written description requirement.

Claims 1, 12, and 14-18 are rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite.

Claims 1, 14, 27, 54-56, and 61 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Healy *et al.* (*Am. J. Physiol.* 280:L1273-1281, 2001).

Claims 12, 15-18, 41-44, and 57-60 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Healy *et al.* in view of Varner and Cheresh (*Curr. Opin. Cell Biol.* 8:724-730, 1996), in further view of Ruoslahti *et al.* (U.S. Pat. No. 6,180,084), in further view of Panzer *et al.* (U.S. Pat. Publication No. 2004/0048253), and in further view of Klinghoffer *et al.* (U.S. Pat. Publication No. 2004/0077574).

VII. ARGUMENT

A. Rejection under 35 U.S.C. § 112, first paragraph, written description

Claims 1, 12, 14-18, 27, 41-44, and 55-61 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the written description requirement. The Office asserts that the application does not provide "support for the specifically claimed steps because there is no description of the combined method steps of claim 1 or any description of assaying the Axl kinase activity for identifying compounds that inhibit angiogenesis" (Office action, June 23, 2008, page 7, paragraph 1). Applicants assert that the specification provides an adequate written description of the pending claims, and further that a literal description of the combined method steps is not required to provide adequate written description. In addition, Applicants point out that the specification specifically describes use of Axl kinase activity to identify compounds that inhibit angiogenesis.

1. Combination of Steps

The Office has not presented a *prima facie* case that one of skill in the art would not understand that Applicants had possession of the invention as claimed at the time of filing of the application. Instead, the Office has merely argued that the application does not literally describe the steps of the pending claims. Applicants assert that a literal description of the combination of two assays for identifying inhibitors of angiogenesis (as in claim 1), the cell-based assay (as in claim 27), or the kinase activity assay (as in claim 56) is *not* required, and even if it is, that the specification provides adequate support for these assays.

Rejection of claims 1, 12, 14-18, and 55

To establish a *prima facie* case of lack of written description, the Office "has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in

the disclosure a description of the invention defined by the claims." *In re Wertheim* 541 F.2d 257, 263 (CCPA 1976). The Office has not met this *prima facie* burden.

Independent claim 1 includes "assaying *in vitro* kinase activity of an Axl polypeptide comprising an amino acid sequence with greater than about 95% identity to full length SEQ ID NO: 4 in the presence of the compound, wherein the Axl polypeptide has kinase activity in the absence of said compound; and performing a cell-based assay in an endothelial cell comprising said Axl polypeptide in the presence of the compound, which assay produces an angiogenesis phenotype in said endothelial cell in the absence of the compound…" The specification describes methods for identifying a compound that inhibits angiogenesis comprising contacting the compound with an Axl polypeptide and determining the functional effect of the compound on the polypeptide (see, *e.g.*, specification, page 2, lines 23-33). Determining the functional effect includes "assaying for a compound that increases or decreases a parameter that is indirectly or directly under the influence of an angiogenesis peptide" and includes enzymatic activity and cell-based angiogenesis phenotypes (including cell proliferation, cell surface marker expression, haptotaxis, and tube formation) (page 8, line 27 to page 9, line 8). Further, assays for identifying modulators of angiogenesis proteins are described on page 30, lines 5-29. The specification states that "any suitable physical, chemical, or phenotypic change that affects activity or binding can be used to assess the influence of a test compound on the polypeptide of this invention" (page 30, lines 20-22).

Further, in the Office action of June 23, 2008, the Office acknowledges that the specification provides "support for Axl, its ligands, expression, and association with diseases…, a general description of an assay to identify inhibitors of angiogenesis/tumorigenesis …, the definition of 'functional effect'…, numerous assays to measure angiogenesis… In one embodiment measurement of integrin cell surface expression is used to identify modulators of angiogenesis …, measuring ligand binding, *cell surface marker expression*, *cellular proliferation*, VEGF-R assays, co-culture assays for *tube formation…*, *haptotaxis*…, CAM assays, cellular morphology…, *kinase activity*…, treatment of HUVEC cells with RNAi directed to Axl inhibits the haptotaxis, proliferation, and tube formation in HUVEC cells…" (Office action of June 23, 2008, paragraph bridging pages 3 to 4, emphasis added). Applicants agree that

the application clearly supports use of these (and other) assays, including Axl kinase activity and cell-based angiogenesis phenotype (as in claim 1 and its dependent claims), to identify inhibitors of angiogenesis. Thus, one of skill in the art would clearly recognize that Applicants had possession of the claimed invention at the time of filing the invention.

In addition to support in the specification for the individual assays set out in pending claim 1, support for the present claims is also found in original claim 1. Original claim 1 recited "a method for identifying a compound that modulates angiogenesis, the method **comprising** the steps of: (i) contacting the compound with an angiogenesis polypeptide…; and (ii) determining the functional effect of the compound upon the angiogenesis polypeptide…" (emphasis added). This claim includes a step of determining a functional effect on Axl; the specification defines determining a functional effect as "assaying for a compound that increases or decreases a parameter that is indirectly or directly under the influence of an angiogenesis protein…" (specification, page 8, lines 27-29). The specification goes on to describe representative assays for measuring such functional effects as including "measuring changes in enzymatic activity; the ability to increase or decrease cellular proliferation, apoptosis, cell cycle arrest, measuring changes in cell surface markers… Determination of the functional effect can also be performed using assays… such as endothelial cell tube formation assays; haptotaxis assays; the chick CAM assay; the mouse corneal assay; VEGF receptor assays, co-culture tube formation assays, and assays that assess vascularization of an implanted tumor" (specification page 8, line 34 to page 9, line 8). Original claim 1 thus encompassed assaying any functional effect described by the specification. There is no indication in the specification that only one functional assay could be used to identify an inhibitor of angiogenesis and the claim was written using the open transition "comprising." Claim 1 as pending merely explicitly sets forth specific functional effects (kinase activity and cell-based angiogenesis phenotype) that can be used to identify inhibitors of angiogenesis. As these specific functional effects are supported by the specification (as acknowledged by the Office), a method that assays more than one of these functional effects is also supported by the specification, particularly as the original claims recited the open transition phrase "comprising." "The transition 'comprising' in a method claim indicates that the claim is open-ended and allows for additional steps." *Invitrogen Corp. v. Biocrest Mfg., L.P.*, 327 F.3d 1364, 1368, 66 USPQ2d 1631, 1634 (Fed. Cir. 2003). Therefore, one of skill in the art would

understand that Applicants had possession of the claimed methods at the time of filing the application.

Finally, there is explicit support in the application for a method for identifying a compound that inhibits angiogenesis by "(i) contacting the compound with an angiogenesis…polypeptide…(ii) determining the physical effect of the compound upon the polypeptide…; and (iii) determining the chemical or phenotypic effect of the compound upon a cell comprising the polypeptide…" (*e.g.*, specification, page 3, lines 17-29). This description provides support for the combination of biochemical assays (such as *in vitro* kinase activity, which would reflect a physical effect of the compound on an Axl polypeptide) and cell-based assays (such as a cell-based assay that produces an angiogenesis phenotype). Thus, one of skill in the art would understand that Applicants had possession of methods including assaying *in vitro* kinase activity of an Axl polypeptide and performing a cell-based assay in a cell comprising the Axl polypeptide to identify a compound that inhibits angiogenesis at the time of filing the application.

The Office particularly asserts that the application does not provide "support for the specifically claimed steps because there is no description of the combined method steps of claim 1" (Office action, June 23, 2008, page 7, paragraph 1). As discussed above, Applicants assert that the application provides adequate support for the method of claim 1. However, *even if* the application did not provide a literal description of the combined assays of claim 1, there is no requirement that the specification explicitly describe every aspect of the claims to provide adequate written description. As established in *Ex parte Parks*, "adequate description under the first paragraph of 35 U.S.C. 112 does not require literal support for the claimed invention… Rather, it is sufficient if the originally-filed disclosure would have conveyed to one having ordinary skill in the art that an appellant had possession of the concept of what is claimed." *Ex parte Parks,* 30 USPQ2d 1234, 1236 (BPAI 1993) (emphasis added). Moreover, the MPEP at § 2163 states "If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met. See, e.g. *Vas-Cath*, 935 F.2d at 1563, 19 USPQ2d at 1116; *Martin v. Johnson,* 454 F.2d 746, 751, 172 USPQ

391, 395 (CCPA 1972) (stating "description need not be in *ipsis verbis* [i.e., "in the same words"] to be sufficient")." Finally, "it is up to the PTO to give reasons why a description not *in ipsis verbis* is insufficient." *In re Wertheim* 541 F.2d 257, 265 (CCPA1976). The Office has not met this burden.

Applicants assert the application describes the particular assays included in claim 1 and that one of skill in the art would readily recognize from the specification that *any combination* of the described assays could be used in methods for identifying compounds that inhibit angiogenesis. The specification describes the use of combinations of assays of functional effects, such as the use of a combination of assays in Figure 13 (effect of Axl RNAi on haptotaxis and β1 integrin expression) and Figure 15 (effect of Axl RNAi on haptotaxis and cell proliferation). Based on the description of combinations of assays in the specification, one of skill in the art would clearly recognize that other combinations of assays (such as kinase activity and cell-based angiogenesis assays, as in current claim 1) could also be used. Thus, even if the application lacked *in ipsis verbis* support for the combination of assays in claim 1 (and claims depending from it), one of skill in the art would understand that Applicants were in possession of the claimed invention at the time of filing of the application.

Rejection of claims 27 and 41-44

Independent claim 27 includes "contacting the compound with an endothelial cell that expresses a recombinant Axl polypeptide comprising an amino acid sequence with greater than about 95% identity to full length SEQ ID NO: 4, wherein the Axl polypeptide has kinase activity in the absence of said compound; and performing a cell-based assay, which assay produces an angiogenesis phenotype in said endothelial cell in the absence of the compound…" As discussed above with respect to independent claim 1 and its dependent claims, the specification provides support for the cell-based assay which produces an angiogenesis phenotype. The specification describes methods for identifying a compound that inhibits angiogenesis comprising contacting the compound with an Axl polypeptide and determining the functional effect of the compound on the polypeptide (see, *e.g.*, specification, page 2, lines 23-33). Determining the functional effect includes "assaying for a compound that increases or decreases a parameter that is indirectly or directly under the influence of an angiogenesis peptide" and includes cell-based angiogenesis

phenotypes (including cell proliferation, cell surface marker expression, haptotaxis, and tube formation) (page 8, line 27 to page 9, line 8). Further, assays for identifying modulators of angiogenesis proteins are described on page 30, lines 5-29. The specification states that "any suitable physical, chemical, or phenotypic change that affects activity or binding can be used to assess the influence of a test compound on the polypeptide of this invention" (page 30, lines 20-22).

Support is also found in original claim 1, which recited "a method for identifying a compound that modulates angiogenesis, the method **comprising** the steps of: (i) contacting the compound with an angiogenesis polypeptide…; and (ii) determining the functional effect of the compound upon the angiogenesis polypeptide…" As discussed above, determining the functional effect includes assaying cell-based angiogenesis phenotype (including cell proliferation, cell surface marker expression, haptotaxis, and tube formation) (page 8, line 27 to page 9, line 8). Further, the Office acknowledged support in the specification for "assessing the modulation of an angiogenesis protein…, numerous assays to measure angiogenesis…[such as] *cell surface marker expression*, *cellular proliferation*, VEGF-R assays, co-culture assays for *tube formation…*, *haptotaxis*…" (Office action of June 23, 2008, paragraph bridging pages 3-4, emphasis added). Applicants agree that the application clearly supports use of these (and other) assays, including cell-based angiogenesis phenotype (as in claim 27 and dependent claims 41-44), to identify inhibitors of angiogenesis. Thus, one of skill in the art would clearly recognize that Applicants had possession of the claimed invention at the time of filing the invention.

In addition to support for the particular assays for determining a functional effect of a compound on an angiogenesis polypeptide such as Axl, the specification provides support for "contacting the compound with a cell that expresses recombinant Axl polypeptide…" The specification describes treating a sample or assay comprising an angiogenesis protein (such as Axl) with a potential modulator to determine the effect of the compound (*e.g.*, specification, page 2, lines 23-32; page 9, lines 32-34) and describes cell-based assays where the protein is expressed in a cell and the protein may be recombinant (*e.g.*, specification page 31, lines 23-32). Thus, one of skill in the art would clearly recognize that Applicants had possession of the claimed subject matter at the time of filing of the application.

Rejection of claims 56-61

Independent claim 56 includes "contacting the compound with an endothelial cell that expresses a recombinant Axl polypeptide comprising an amino acid sequence with greater than about 95% identity to full length SEQ ID NO: 4, wherein the Axl polypeptide has kinase activity in the absence of said compound; and assaying the kinase activity of the Axl polypeptide..." As discussed above with respect to independent claim 1 and its dependent claims, the specification provides support for assaying Axl kinase activity. The specification describes methods for identifying a compound that inhibits angiogenesis comprising contacting the compound with an Axl polypeptide and determining the functional effect of the compound on the polypeptide (see, *e.g.*, specification, page 2, lines 23-33). Determining the functional effect includes "assaying for a compound that increases or decreases a parameter that is indirectly or directly under the influence of an angiogenesis peptide" and includes enzymatic activity (page 8, line 27 to page 9, line 1), which would include kinase activity. Further, assays for identifying modulators of angiogenesis proteins are described on page 30, lines 5-29. The specification states that "any suitable physical, chemical, or phenotypic change that affects activity or binding can be used to assess the influence of a test compound on the polypeptide of this invention" (page 30, lines 20-22).

Support is also found in original claim 1, which recited "a method for identifying a compound that modulates angiogenesis, the method **comprising** the steps of: (i) contacting the compound with an angiogenesis polypeptide...; and (ii) determining the functional effect of the compound upon the angiogenesis polypeptide..." As discussed above, determining the functional effect includes assaying cell-based angiogenesis phenotype (including cell proliferation, cell surface marker expression, haptotaxis, and tube formation) (page 8, line 27 to page 9, line 8). Further, the Office acknowledged support in the specification for "assessing the modulation of an angiogenesis protein..., numerous assays to measure angiogenesis... [such as] *kinase activity...*" (Office action of June 23, 2008, paragraph bridging pages 3-4). Applicants agree that the application clearly supports use of these (and other) assays, including Axl kinase activity (as in claim 56 and its dependent claims), to identify inhibitors of angiogenesis. Thus,

one of skill in the art would clearly recognize that Applicants had possession of the claimed invention at the time of filing the invention.

In addition to support for the particular assays for determining a functional effect of a compound on an angiogenesis polypeptide such as Axl, the specification provides support for "contacting the compound with a cell that expresses recombinant Axl polypeptide..." The specification describes treating a sample or assay comprising an angiogenesis protein (such as Axl) with a potential modulator to determine the effect of the compound (*e.g.*, specification, page 2, lines 23-32; page 9, lines 32-34) and describes cell-based assays where the protein is expressed in a cell and the protein may be recombinant (*e.g.*, specification page 31, lines 23-32). Thus, one of skill in the art would clearly recognize that Applicants had possession of the claimed subject matter at the time of filing of the application.

2. Kinase Activity

The Office also asserts that the specification lacks support for assaying Axl kinase activity to identify inhibitors of angiogenesis (Office action of June 23, 2008, page 7, 1st paragraph). Applicants assert that the specification clearly describes determining Axl kinase activity to identify angiogenesis inhibitors. As a preliminary matter, Axl was well known as a tyrosine kinase receptor at the time of filing of the application (see, *e.g.,* specification page 6, lines 9-11).

Rejection of claims 1, 12, 14-18, and 55

The specification describes assaying for a compound that modulates angiogenesis by determining "a parameter that that is indirectly or directly under the influence of an angiogenesis polypeptide" (page 8, lines 15-18). Axl is defined by the specification as an angiogenesis polypeptide (see, *e.g.*, page 5, lines 22-23 and page 6, lines 8-9) and as a receptor tyrosine kinase (page 6, line 9). Without more, one of skill in the art would clearly recognize that Axl kinase activity is a parameter under the influence of Axl. In addition, the specification further describes the parameters that are to be assayed as including enzymatic activity (see, *e.g.*, page 8, line 22; page 8 line 34 to page 9, line 1; page 31, lines 26-27), which a person of skill in the art would recognize to include Axl kinase activity. Further, *the Office acknowledges* that the specification

supports use of kinase activity to identify modulators of angiogenesis (Office action, page 4, line 8). Therefore, one of skill in the art would certainly recognize that assaying Axl kinase activity (as in claim 1 and its dependent claims) for identifying inhibitors of angiogenesis was in possession of the inventors at the time of filing.

Rejection of claims 56-61

The arguments above with regard to support in the specification for determining Axl kinase activity to identify angiogenesis inhibitors also apply to independent claim 56 and its dependent claims. One of skill in the art would clearly recognize that assaying Axl kinase activity for identifying inhibitors of angiogenesis was in possession of the inventors at the time of filing.

3. Axl Polypeptide Comprising SEQ ID NO: 4

Claims 1, 12, 14-18, 27, 41-44, and 55-61

The Office asserts that the application does not support "an Axl polypeptide comprising SEQ ID NO: 4 which encompasses sequences outside of SEQ ID NO: 4" (Office action, page 4, last paragraph). Each independent claim (1, 27, and 56) includes this phrase, and the arguments below apply equally to each of the independent claims and their dependent claims.

Applicants assert that the specification provides clear support for an Axl polypeptide comprising SEQ ID NO: 4 (or a sequence with greater than about 95% identity to full length SEQ ID NO: 4) which encompasses additional sequences or other elements outside of SEQ ID NO: 4. For example, the specification describes labels which may be incorporated into a protein (page 16, lines 6-11) and fusion proteins (page 16, lines 24-26 and page 27, lines 20-25). Such labels and fusion proteins were well known in the art at the time of filing of the present application. Therefore, there is support in the specification for an Axl polypeptide which comprises SEQ ID NO: 4 and additional elements.

Applicants also assert that even in the absence of explicit support for additional sequences or elements outside of SEQ ID NO: 4, the open transitional language "comprising" provides adequate support. The Written Description Training Materials (Revision 1, March 25,

2008) in Example 4A discusses the effect of open transitional language, such as that of the present claims. Example 4A describes a specification disclosing SEQ ID NO: 16 and a claim reciting "an isolated DNA comprising SEQ ID NO: 16." The training materials indicate that although the sequence could be combined with other sequences, "the scope of the genus is defined by the presence of the structure shown in SEQ ID NO: 16. Thus all members of the genus will predictably include SEQ ID NO: 16… Because SEQ ID NO: 16 is a structural feature common to all members of the genus and the specification describes the complete structure (sequence) of SEQ ID NO: 16, one skilled in the art would recognize that the applicant was in possession of a common structural feature of members of the genus." The example goes on to conclude that the specification satisfies the written description requirement with respect to this claim.

The present situation is directly analogous to Example 4A. Applicants' specification discloses the amino acid sequence SEQ ID NO: 4 and the claims recite "an Axl polypeptide comprising an amino acid sequence with greater than about 95% identity to full length SEQ ID NO: 4…" Therefore, the specification provides adequate written description for an Axl polypeptide including the structure shown in SEQ ID NO: 4 (or with greater than about 95% identity to full length SEQ ID NO: 4) even in combination with additional sequences (or other structural elements) attached to either end of SEQ ID NO: 4.

B. Rejection under 35 U.S.C. § 112, second paragraph

Claims 1, 12, and 14-18 stand rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite. The Office asserts that these claims are indefinite for omitting the allegedly essential step of "contacting the Axl polypeptide or cell comprising the Axl polypeptide with the compound being examined" (Office action of June 23, 2008, page 9).

Applicants first point out that "a claim which omits matter disclosed to be essential to the invention as described in the specification…may be rejected under 35 U.S.C. § 112, first paragraph *as not enabling*." MPEP § 2172.01, emphasis added (citing *In re Mayhew,* 527 F.2d 1229 (CCPA 1976)). Therefore, this rejection is not properly raised under 35 U.S.C. § 112, second paragraph.

Even if this rejection were properly made, the proper standard must be applied. "Determining whether a claim is definite requires an analysis of whether one skilled in the art would understand the bounds of the claim when read in light of the specification. If the claims read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, § 112 demands no more." *Solomon v. Kimberly-Clark Corporation* 216 F.3d 1372, 1378 (Fed. Cir. 2000). Further, "[t]he requirement to 'distinctly' claim means that the claim must have a meaning discernible to one of ordinary skill in the art when construed according to correct principles… Only when a claim remains insolubly ambiguous without a discernible meaning after all reasonable attempts at construction must a court declare it indefinite." *Metabolite Labs, Inc. v. Lab Corp. of Am. Holdings* 370 F.3d 1354, 1366 (Fed. Cir. 2004).

Applicants assert the claims have a discernible meaning to one of skill in the art and are therefore definite. Claim 1 recites "assaying *in vitro* kinase activity of an Axl polypeptide comprising an amino acid sequence with greater than about 95% identity to full length SEQ ID NO: 4 *in the presence of the compound*, wherein the Axl polypeptide has kinase activity in the absence of said compound; and performing a cell-based assay in an endothelial cell comprising said Axl polypeptide *in the presence of the compound*, which assay produces an angiogenesis phenotype in said endothelial cell in the absence of the compound…" This claim has a clearly discernible meaning to one of skill in the art and does not omit essential matter (that is, it is enabled) nor fail to interrelate essential elements of the invention (that is, the claim is definite). Further, claim 1 recites "wherein inhibition of the *in vitro* kinase activity of the Axl polypeptide *in the presence of the compound* and inhibition of the angiogenesis phenotype in the cell-based assay *in the presence of the compound* identifies the compound as a compound that inhibits angiogenesis" (emphasis added).

Claim 1 thus sets forth that the assay is to be performed in the presence of a test compound. Further, the specification sets forth that "samples or assays comprising angiogenesis or tumorigenesis proteins that are treated with a potential activator, inhibitor, or modulator are compared to control samples without the inhibitor, activator, or modulator to examine the extent of inhibition" (page 9, lines 32-34). Therefore, when claim 1 is read in light of the specification,

one of skill in the art would readily understand that the assays are performed in the presence of the compound. It is not essential that the claim recite a step of contacting an Axl polypeptide or the cell comprising an Axl polypeptide with the compound. Claim 1 (and dependent claims 12 and 14-18) clearly set forth the metes and bounds of the claim and apprises one of skill in the art of the scope of the invention. In other words, the claims have a discernible meaning to one of skill in the art when read in light of the specification, and are therefore definite.

C. Rejection under 35 U.S.C. § 102(b)

Claims 1, 14, 27, 54-56, and 61 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Healy *et al.* (*Am. J. Physiol.* 280:L1273-1281, 2001).

Rejection of claims 1, 14, 54, and 55

The Office alleges that Healy *et al.* teach "determining the *in vitro* kinase activity of an Axl polypeptide…[,] performing a cell-based assay in an endothelial cell… and determining the effect of this interaction on cell number…" as well as teaching assaying apoptosis in endothelial cells expressing Axl (Office action of June 23, 2008, page 10, second paragraph). The Office further asserts that as Healy allegedly "comprises the same method steps as claimed in the instant invention, determining *in vitro* kinase activity of an Axl polypeptide…; and performing a cell based assay in an endothelial cell comprising said Axl polypeptide… the claimed method is anticipated because the method will *inherently* be a method for identifying a compound that inhibits angiogenesis…" (Office action, paragraph bridging pages 10-11, emphasis added).

A rejection under 35 U.S.C. § 102 is appropriate "only if each and every element as set forth in the claim is found, either expressly or inherently described in a single prior art reference." MPEP § 2131. Further, "the prior art reference – in order to anticipate under 35 U.S.C. § 102 – must not only disclose all elements of the claim within the four corners of the document, but must also disclose those elements 'arranged as in the claim.'" *Net MoneyIN, Inc. v. Verisign Inc.* Fed. Cir., Appeal No. 2007-1565, October 20, 2008, emphasis added.

Importantly, Healy *et al.* do not teach the *combination* of assaying *in vitro* kinase activity of an Axl polypeptide in the presence of a test compound *and* performing a cell-based assay in

the presence of the compound which produces an angiogenesis phenotype in the absence of the test compound, as in claim 1. In order to anticipate the claims, the reference must disclose the limitations arranged as they are in the claim. This "refers to the need for an anticipatory reference to show all of the limitations of the claims *arranged or combined in the same way* as recited in the claims..." *Net MoneyIN, Inc. v. Verisign Inc.* Fed. Cir., Appeal No. 2007-1565, October 20, 2008, emphasis added. Thus, in order for Healy *et al.* to anticipate claim 1, it must teach the combination of assays as it is found in Applicants' claim. However, while Healy *et al.* describe that contacting human pulmonary artery endothelial cells (HPAEC), which express Axl polypeptide, with exogenous Gas 6 (an Axl ligand) increased Axl phosphorylation (page L1276, column 2 and Figure 5), increased cell number (page L1276, column 2 and Figure 6), and decreased apoptosis of the cells in serum free medium (page L1277, column 2; page 1278, column 2; Figures 8 and 10), these assays are all described independently. Nowhere, does Healy *et al.* describe combining these assays, let alone that these assays would identify or could be used to identify an inhibitor of angiogenesis. Thus, Healy *et al.* does not anticipate claim 1 or dependent claims 14, 54, and 55.

Further, Healy *et al. do not* teach that Gas 6 (an Axl polypeptide agonist) is an angiogenesis inhibitor. This has been previously noted by Applicants (Office action response of February 23, 2007, page 15, third paragraph). This has also been *admitted by the Office*, which stated "Healy does not teach that Gas 6 specifically inhibits angiogenesis..." (Office action of May 7, 2007, page 11, third paragraph). Further, Healy *et al.* do not teach contacting Axl or cells comprising Axl with any compound other than Gas 6. In the Office action of May 7, 2007, the Office attempted to cure the deficiencies of Healy *et al.* by asserting that Gallicchio *et al.* (*Blood* 105:1970-1976, 2005; cited in the Office action of May 7, 2007) provides evidence that Gas 6 inhibits angiogenesis upon interacting with Axl (Office action of May 7, 2007, page 12, first paragraph), and that Healy *et al.* thus inherently anticipates Applicants' claims. Applicants assert that Gallicchio *et al.* does not provide evidence that Healy *et al.* inherently anticipates claims 1, 14, 54, and 55.

"The fact that a certain result or characteristic <u>may</u> occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic ... Inherency, however,

may not be established by probabilities or possibilities." MPEP § 2112. To show inherency, a gap in a reference may be filled by extrinsic evidence, but the "evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *Continental Can Co. USA v. Monsanto Co.,* 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991); MPEP § 2131.01, emphasis added. Applicants strongly assert that Healy *et al.* does not expressly anticipate the claimed methods, nor has the Office has not provided any extrinsic evidence to make it clear that Healy *et al.* necessarily inherently anticipates the claims. Instead, Gallichio *et al.*, the only evidence proffered by the Office, makes it clear that Healy *et al.* do not anticipate any of the present claims.

Based on Gallicchio *et al.*, one of skill in the art would predict that *inhibition* of Axl polypeptide activity would *stimulate* activation of an angiogenic program in vascular endothelial cells. Gas 6 *stimulates* Axl polypeptide activity, which inhibits activation of vascular endothelial growth factor receptor 2 (VEGFR2) and leads to *inhibition* of an angiogenic program in vascular endothelial cells (Gallicchio *et al.,* abstract; page 1973, first full paragraph; Figure 4A). Therefore, based on Gallicchio *et al.,* one of skill in the art would predict that *inhibition* of Axl would activate VEGFR2 and lead to *stimulation* of angiogenesis. Thus, the expected effect of Healy *et al.* would be the *opposite* of Applicants' demonstrated inhibition of angiogenesis by inhibition of Axl. As Gas 6 is not an inhibitor of Axl, Healy *et al.* do not expressly or inherently teach the claimed method for identifying a compound that is an inhibitor of angiogenesis and therefore this reference does not anticipate any of the claims (including independent claims 1, 27, and 56 and any claims that depend from these claims).

Applicants point out that the foregoing discussion was previously presented in the amendment of October 5, 2007 and it was tacitly acknowledged and accepted as persuasive by the Office, which withdrew this rejection (of all claims) without comment in the Office action of December 12, 2007. Applicants emphasize that this rejection under 35 U.S.C. § 102(b) has previously been overcome and that Healy *et al.* still does not anticipate the claims.

Rejection of claims 27 and 54

The Office alleges that Healy *et al.* teach "determining the *in vitro* kinase activity of an Axl polypeptide…[,] performing a cell-based assay in an endothelial cell… and determining the effect of this interaction on cell number…" as well as teaching assaying apoptosis in endothelial cells expressing Axl (Office action of June 23, 2008, page 10, second paragraph). The Office further asserts that as Healy allegedly "comprises the same method steps as claimed in the instant invention, determining *in vitro* kinase activity of an Axl polypeptide…; and performing a cell based assay in an endothelial cell comprising said Axl polypeptide… the claimed method is anticipated because the method will *inherently* be a method for identifying a compound that inhibits angiogenesis…" (Office action, paragraph bridging pages 10-11, emphasis added).

Healy *et al. do not* teach that Gas 6 (an Axl polypeptide agonist) is an angiogenesis inhibitor. This has been previously noted by Applicants (Office action response of February 23, 2007, page 15, third paragraph, and above). This has also been *admitted by the Office*, which stated "Healy does not teach that Gas 6 specifically inhibits angiogenesis…" (Office action of May 7, 2007, page 11, third paragraph). Further, Healy *et al.* do not teach contacting Axl or cells comprising Axl with any compound other than Gas 6. In the Office action of May 7, 2007, the Office attempted to cure the deficiencies of Healy *et al.* by asserting that Gallicchio *et al.* (*Blood* 105:1970-1976, 2005; cited in the Office action of May 7, 2007) provides evidence that Gas 6 inhibits angiogenesis upon interacting with Axl (Office action of May 7, 2007, page 12, first paragraph) and that Healy *et al.* thus inherently anticipates Applicants' claims.

As discussed above, based on Gallicchio *et al.*, one of skill in the art would predict that *inhibition* of Axl polypeptide activity would *stimulate* activation of an angiogenic program in vascular endothelial cells. Gas 6 *stimulates* Axl polypeptide activity, which inhibits activation of vascular endothelial growth factor receptor 2 (VEGFR2) and leads to *inhibition* of an angiogenic program in vascular endothelial cells (Gallicchio *et al.,* abstract; page 1973, first full paragraph; Figure 4A). Therefore, based on Gallicchio *et al.*, one of skill in the art would predict that *inhibition* of Axl would activate VEGFR2 and lead to *stimulation* of angiogenesis. Thus, the expected effect of Healy *et al.* would be the *opposite* of Applicants' demonstrated inhibition of angiogenesis. As Gas 6 is not an inhibitor of Axl, Healy *et al.* do not expressly or inherently

teach the claimed method of identifying a compound that is an inhibitor of angiogenesis and therefore this reference does not anticipate any of the claims (including independent claims 1, 27, and 56 and any claims that depend from these claims).

Rejection of claims 56 and 61

Finally, the Office states that "'determining the functional effects of the compound upon the kinase activity of the Axl polypeptide,' when given its broadest reasonable interpretation encompasses assaying cellular responses such as increases or decreases in cellular proliferation and apoptosis" (Office action of June 23, 2008, page 10, third paragraph). Applicants point out that this language ("determining the functional effect") is no longer present in independent claims 1, 27, or 56. Claim 56 currently recites "assaying the kinase activity of the Axl polypeptide" to identify a compound that inhibits angiogenesis. Healy *et al.* teach only assaying the effect of Gas 6 on Axl kinase activity. As discussed above, Healy et al. do not teach that Gas 6 is an inhibitor of Axl, when read in light of Gallicchio *et al.* Thus, Healy *et al.* do not expressly or inherently teach the claimed method of identifying a compound that is an inhibitor of angiogenesis and this reference does not anticipate claims 56 or 61.

D. Rejection under 35 U.S.C. § 103(a)

Claims 12, 15-18, 41-44, and 57-60 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Healy *et al.* in view of Varner and Cheresh (*Curr. Opin. Cell Biol.* 8:724-730, 1996), in further view of Ruoslahti *et al.* (U.S. Pat. No. 6,180,084), in further view of Panzer *et al.* (U.S. Pat. Publication No. 2004/0048253), and in further view of Klinghoffer *et al.* (U.S. Pat. Publication No. 2004/0077574). Claims 12, 15-18, 41-44, and 57-60 each depend from claim 1, 27, or 56.

To establish a *prima facie* case of obviousness, the Office must establish that (1) there is some suggestion or motivation to combine the references, either in the references or in common general knowledge of one of skill in the art (MPEP § 2143.01); and (2) there is a reasonable expectation of success (MPEP § 2143.02). In addition, the Office must show that the references teach or suggest all claim limitations. "When determining whether a claim is obvious, an Examiner must make 'a searching comparison of the claimed invention – *including all its*

limitations – with the teaching of the prior art.' Thus, 'obviousness requires a suggestion of all limitations in a claim.'" *Ex parte Mumper* BPAI, Appeal No. 2008-2332, June 27, 2008.

Based on the discussion of Healy *et al.* above, Applicants maintain that Healy *et al.* do not teach all the limitations of the claims, namely that Healy *et al.* do not teach or even suggest identification of an inhibitor of angiogenesis. Further, Healy *et al.* make no suggestion that Axl polypeptide plays a role in angiogenesis. Rather, Healy *et al.* teach only that Axl and its ligand Gas 6 have anti-apoptotic activity in HPAEC cells and that this may be "relevant to endothelial cell survival in the quiescent environment of the vessel wall" (Healy *et al.*, abstract).

The Office alleges that Varner and Cheresh teach a role for integrin $\alpha v\beta 3$ in angiogenesis. However, Varner and Cheresh do not teach or suggest a role for Axl polypeptide in angiogenesis nor selecting a compound that inhibits *in vitro* kinase activity of Axl polypeptide and inhibits angiogenesis phenotype in a cell-based assay to identify inhibitors of angiogenesis. Therefore, this reference does not cure the deficiencies of Healy *et al.* Likewise, Panzer *et al.* and Ruoslahti *et al.* teach only general methods of screening small molecules and other compounds for use in diagnosis or therapy. There is no discussion of Axl polypeptide in these references; therefore they cannot cure the deficiencies of Healy *et al.* Klinghoffer *et al.* teach only use of siRNAs for altering gene expression. This reference discloses Axl only as containing a potential protein tyrosine phosphatase 1B recognition motif (Klinghoffer *et al.*, paragraph [0016]) and does not teach or suggest a role for Axl polypeptide in angiogenesis. Therefore Klinghoffer *et al.* cannot be used to cure the deficiencies of Healy *et al.*

The Office does not provide any rationale for one of skill in the art to combine or modify the cited references. Taken together, one of skill might be motivated to assay regulation of apoptosis by Axl, but not regulation of angiogenesis. However, Applicants' claims are based on the novel recognition that inhibition of Axl polypeptide inhibits angiogenesis. None of the cited references disclose that Axl has any role in angiogenesis, nor suggest that inhibitors of Axl could be inhibitors of angiogenesis. Without the recognition that inhibition of Axl inhibits angiogenesis, there is no motivation to combine the references and no expectation of success in

arriving at Applicants' claimed invention by combining the references. Thus, alone or in combination, the cited references do not support a *prima facie* case of obviousness.

In sum, none of the references cited by the Office teach or suggest, either alone or in combination, all of the features of Applicants' claims. It remains well-settled law that obviousness requires at least a suggestion of all of the features in a claim. *See Ex parte Mumper* (BPAI, Appeal 2008-2332, June 27, 2008) citing *CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003) and *In re Royka*, 490 F.2d 981, 985 (CCPA 1974). The Office has not met this burden and has not provided any "*articulated reasoning* with some rational underpinning to support the legal conclusion of obviousness." *KSR Int'l v. Teleflex*, 127 S. Ct. 1727, 1741 (2007) (*quoting In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006).

E. Conclusion

Applicants have shown that the claims are supported by adequate written description.

- One of skill in the art would recognize that the specification describes use of numerous assays, including kinase activity and cell-based angiogenesis phenotype assays, to identify inhibitors of angiogenesis, separately or in combination (as in independent claims 1, 27, and 56).
- The specification specifically includes assaying kinase activity of an angiogenesis polypeptide, such as Axl, to identify compounds that inhibit angiogenesis (as in independent claims 1 and 56).
- The use of the transitional phrase "comprising" supports polypeptides including a sequence with greater than about 95% identity to full length SEQ ID NO: 4 plus additional sequences or elements (as in independent claims 1, 27, and 56).

Applicants have shown that when read in light of the specification, claims 1, 12, and 14-18 have a discernible meaning to one of skill in the art and are therefore definite.

Applicants have shown that Healy *et al.* does not anticipate the claims.

- Healy *et al.* do not teach the use of the *combination* of assaying Axl kinase activity and a cell-based angiogenesis assay to identify compounds that inhibit angiogenesis, as in independent claim 1.
- Healy *et al.* do not teach that the Axl ligand Gas6 is an inhibitor of Axl or an inhibitor of angiogenesis, and Gallicchio *et al.* does not provide any extrinsic evidence that Healy *et al.* necessarily anticipates the claims (including independent claims 1, 27, and 56).

Applicants have shown that none of the references cited by the Office teach or suggest, either alone or in combination, all of the features of claims 12, 15-18, 41-44, or 57-60. Therefore, the claims are not obvious in light of the cited references.

In view of the above remarks, Applicants believe that they have overcome the rejection of claims 1, 12, 14-18, 27, 41-44, and 55-61 under 35 U.S.C. § 112, first paragraph; the rejection of claims 1, 12, and 14-18 under 35 U.S.C. § 112, second paragraph; the rejection of claims 1, 14, 27, 54-56, and 61 under 35 U.S.C. § 102(b); and the rejection of claims 12, 15-18, 41-44, and 57-60 under 35 U.S.C. § 103(a). Applicants request that the rejection of claims 1, 12, 14-18, 27, 41-44, and 54-61 be withdrawn.

Respectfully submitted,

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Claims Appendix

1. (Rejected) A method for identifying a compound that inhibits angiogenesis, the method comprising:

assaying *in vitro* kinase activity of an Axl polypeptide comprising an amino acid sequence with greater than about 95% identity to full length SEQ ID NO: 4 in the presence of the compound, wherein the Axl polypeptide has kinase activity in the absence of said compound; and

performing a cell-based assay in an endothelial cell comprising said Axl polypeptide in the presence of the compound, which assay produces an angiogenesis phenotype in said endothelial cell in the absence of the compound,

wherein inhibition of the *in vitro* kinase activity of the Axl polypeptide in the presence of the compound and inhibition of the angiogenesis phenotype in the cell-based assay in the presence of the compound identifies the compound as a compound that inhibits angiogenesis.

2-11. (Canceled)

12. (Rejected) The method of claim 1, wherein the angiogenesis phenotype is $\alpha v\beta 3$ expression, tube formation or haptotaxis.

13. (Canceled)

14. (Rejected) The method of claim 1, wherein the polypeptide is recombinant.

15. (Rejected) The method of claim 1, wherein the compound is an antibody.

16. (Rejected) The method of claim 1, wherein the compound is an antisense molecule.

17. (Rejected) The method of claim 1, wherein the compound is an RNAi molecule.

18. (Rejected) The method of claim 1, wherein the compound is a small organic molecule.

19-26. (Canceled)

27. (Rejected) An *in vitro* method for identifying a compound that inhibits angiogenesis, the method comprising:

contacting the compound with an endothelial cell that expresses a recombinant Axl polypeptide comprising an amino acid sequence with greater than about 95% identity to full length SEQ ID NO: 4, wherein the Axl polypeptide has kinase activity in the absence of said compound; and

performing a cell-based assay, which assay produces an angiogenesis phenotype in said endothelial cell in the absence of the compound,

wherein inhibition of the angiogenesis phenotype in the cell-based assay in the presence of the compound identifies the compound as a compound that inhibits angiogenesis.

28-40. (Canceled)

41. (Rejected) The method of claim 27, wherein the compound is an antibody.

42. (Rejected) The method of claim 27, wherein the compound is an antisense molecule.

43. (Rejected) The method of claim 27, wherein the compound is an RNAi molecule.

44. (Rejected) The method of claim 27, wherein the compound is a small organic molecule.

45-53. (Canceled)

54. (Rejected) The method of claim 1 or 27, wherein the Axl polypeptide comprises SEQ ID NO: 4.

55. (Rejected) The method of claim 1, wherein inhibition of the angiogenesis phenotype in the cell-based assay is caused by down regulation of expression of the Axl polypeptide.

56. (Rejected) A method for identifying a compound that inhibits angiogenesis, the method comprising:

contacting the compound with a cell expressing a recombinant Axl polypeptide comprising an amino acid sequence with greater than about 95% identity to full length SEQ ID NO: 4, wherein the Axl polypeptide has kinase activity in the absence of said compound; and

assaying the kinase activity of the Axl polypeptide,

wherein inhibition of the kinase activity of the Axl polypeptide in the presence of the compound identifies the compound as a compound that inhibits angiogenesis.

57. (Rejected) The method of claim 56, wherein the compound is an antibody.

58. (Rejected) The method of claim 56, wherein the compound is an antisense molecule.

59. (Rejected) The method of claim 56, wherein the compound is an RNAi molecule.

60. (Rejected) The method of claim 56, wherein the compound is a small organic molecule.

61. (Rejected) The method of claim 56, wherein the Axl polypeptide comprises SEQ ID NO: 4.

Evidence Appendix

1. Healy *et al.* "Gas6 Promotes Axl-Mediated Survival in Pulmonary Endothelial Cells" *Am. J. Physiol. Lung Cell Mol. Physiol.* 280:L1273-L1281, 2001; cited in the Office Actions dated August 23, 2006, May 7, 2007, and June 23, 2008

2. Gallicchio *et al.* "Inhibition of Vascular Endothelial Growth Factor Receptor 2-Mediated Endothelial Cell Activation by Axl Tyrosine Kinase Receptor" *Blood* 105:1970-1976, 2005; cited in the Office Actions dated May 7, 2007 and June 23, 2008

3. Varner and Cheresh "Integrins and Cancer" *Curr. Opin. Cell Biol.* 8:724-730, 1996; cited in the Office Actions dated August 23, 2206, May 7, 2007, and June 23, 2008

4. Ruoslahti *et al.,* U.S. Pat. No. 6,180,084; cited in the Office Actions dated August 23, 2006, May 7, 2007, and June 23, 2008

5. Panzer *et al.*, U.S. Pat. Publication No. 2004/0048253; cited in the Office Actions dated August 23, 2006, May 7, 2007, and June 23, 2008

6. Klinghoffer *et al.* U.S. Pat. Publication No. 2004/0077574; cited in the Office Action dated June 23, 2008

Related Proceedings Appendix

There are no related proceedings.